

REMARKS/ARGUMENTS

The foregoing amendments in the specification and claims are of a formal nature, and do not add new matter.

Prior to the present amendment, Claims 28-47 were pending in this application and were rejected on various grounds. With this amendment, Claims 36-37 and 41-43 have been canceled without prejudice, Claims 28-35, 38-39 and 44 have been amended, and new Claims 48-57 have been added.

Claims 28-35, 38-40 and 44-57 are pending after entry of the instant amendment. Applicants expressly reserve the right to pursue any canceled matter in subsequent continuation, divisional or continuation-in-part applications.

The amendments to the specification and claims are fully supported by the specification and claims as originally filed and do not constitute new matter. In addition, new Claims 48-57 are fully supported by the specification as originally filed. Amendments to Claims 28-32 can be found in Example 150 at least on page 512, line 12 of the specification. Support new Claims 48-52 can be found at least in Example 141, starting on page 492, line 32 of the specification. Support for new Claims 53-57 can be found at least in Example 149, starting on page 511, line 34 of the specification.

In addition, Applicants request the PTO to take note of the Revocation and Power of Attorney and Change of Address filed on February 28, 2003, and kindly direct all future correspondence to the address indicated, *i.e.*, to:

CUSTOMER NO. 35489
Ginger R. Dreger
Heller Ehrman White & McAuliffe LLP
275 Middlefield Road
Menlo Park, California 94025
Telephone: (650) 324-7000
Facsimile: (650) 324-0638

1. Formal Matters

Applicants thank the Examiner for entering the Preliminary Amendment filed on December 12, 2001 into the record.

2. Priority

The Examiner alleges that "[d]ue to the excessive number of applications from which the present application claims benefit, priority cannot be determined."

The Examiner's attention is respectfully directed to the Preliminary Amendment filed on August 29, 2002, which states that the present application is "a continuation of, and claims priority under 35 U.S.C. §120 to, PCT Application PCT/US00/04342 filed 2/18/2000, which is a continuation-in-part of, and claims priority under 35 U.S.C. §120 to, U.S. Patent Application Serial No. 09/403,297 filed 10/18/1999, now abandoned, which is the National Stage filed under 35 U.S.C. §371 of PCT Application PCT/US99/20111 filed 9/1/1999, which claims priority under 35 U.S.C. §119 to US Provisional Application Serial No. 60/101,479 filed 9/23/1998."

As discussed below, Applicants further rely on the chondrocyte re-differentiation assay (Example 150, Assay 110), the skin vascular permeability assay (Example 141, Assay 64) and the glucose/FFA uptake assay (Example 149, Assay 94) for patentable utility which were first disclosed in PCT/US00/04342 filed on February 18, 2000, priority to which has been claimed in this application. Accordingly, the present application is entitled to at least the February 18, 2000 priority. In support, Applicants enclose herewith page 504, describing the skin vascular permeability assay (Example 141) and page 523, describing the chondrocyte re-differentiation assay (Example 150) and the glucose/FFA uptake assay (Example 149) of the PCT Publication WO 00/78961, corresponding to PCT Application PCT/US00/04342.

3. Information Disclosure Statement

Applicants note that the Examiner did not enter the Information Disclosure Statement filed on September 12, 2002 was not made of record. Therefore, Applicants respectfully request that the Information Disclosure Statement filed on September 12, 2002 be considered by the

Examiner and be made of record in the above-identified application.

In response to an anticipated assertion by the Examiner that references 1 and 2 in the Information Disclosure Statement filed on September 12, 2002 are not in proper format, Applicants file herewith, an Information Disclosure Statement listing each reference of the "Blast Search" separately and including authors/inventors, relevant accession numbers and publication dates. Applicants respectfully request that the listed information be considered by the Examiner and be made of record in the above-identified application.

4. Specification

As requested by the Examiner, the specification has been amended to remove embedded hyperlink and/or other form of browser-executable code, and the title of the application has been amended to recite a new, descriptive title indicative of the invention to which the claims are directed.

The Examiner objects to the specification since the status of U.S. Patent Application Serial No. 09/380,137 should be updated to "now abandoned". Applicants respectfully submit that the instant specification does not refer to U.S. Patent Application Serial No. 09/380,137. Further, the Examiner's attention is respectfully directed to the Preliminary Amendment filed on August 29, 2002, , which does not claims priority to the U.S. Patent Application Serial No. 09/380,137.

5. Claim Objections

Claims 28-47 were objected to for reciting a Figure number and a SEQ ID NO. Applicants submit that the cancellation of Claims 36-37 and 41-43 renders the objection to these claims moot. Further, Applicants submit that Claims 28-35 and 38-39 have been amended to only recite SEQ ID NO. Accordingly, Applicants respectfully request that the Examiner withdraw the objection to Claims 28-35, 38-40 and 44-47.

6. Claim Rejections Under 35 U.S.C. §112, First Paragraph (Enablement)

A. Claims 28-47 stand rejected under 35 U.S.C. §112, first paragraph, allegedly for

"containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention." The Examiner specifically notes that "the deposit of the biological material is considered necessary for the enablement of the current invention."

Applicants submit that the cancellation of Claims 36 and 37 renders the rejection of these claims moot.

Applicants disagree with the Examiner's assertion that the deposit was necessary for enablement of the current invention. The current invention is fully enabled by the disclosure of the present application, including the sequence of PRO1325 and its coding sequence. Further, as discussed above, the foregoing amendment to the specification corrects the address of ATCC, and further elaborates on the conditions of the deposit, which was made for patent purposes, under the terms of the Budapest treaty.

Nevertheless, Applicants enclose herewith a copy of the deposit receipt indicating that DNA66659-1593 deposit, ATCC Deposit No. 203269, was made by Applicants on September 22, 1998.

In addition, Applicants respectfully submit that the specification clearly discloses that the deposit was made under the Budapest Treaty and provides the accession number for the deposit, the date of the deposit, the description of the deposited material, and the name and address of the depository starting on page 517, line 1 of the specification.

Applicants further submit that the specification has been amended to recite that the deposit will be maintained "for 30 years from the date of deposit and for at least five (5) years after the most recent request for the furnishing of a sample of the deposit received by the depository" and to recite that "all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of the pertinent U.S. patent."

Accordingly, Applicants believe that the present rejection should be withdrawn.

B. The Examiner further alleges that even if a deposit is made under the terms of the

Budapest Treaty, which Applicants assert they do, "Claims 28-47 would still be rejected under 35 U.S.C. §112, first paragraph, because the specification, while then being enabling for SEQ ID NO:226 and 227, does not reasonably provide enablement for polynucleotides or polypeptides having at least 80%, 85%, 90%, 95% or 99% sequence identity to SEQ ID NO:226 or 227, to the protein encoded by ATCC No. 203269, for the extracellular domain thereof, or for vectors and host cells containing these polynucleotides." In addition, the Examiner alleges that "[t]he claims are broad ... because the claims have no functional limitation."

Applicants respectfully disagree and traverse the rejection.

Without acquiescing to the Examiner's position, and solely in the interest of expediting prosecution in this case, Claims 28-32 (and, as a consequence, those claims dependent from the same) have been amended to recite a functional limitation wherein the encoded polypeptide "induces chondrocyte re-differentiation." Applicants submit that the specification provides ample enablement for such polypeptides based on the *in vitro* data provided in the chondrocyte re-differentiation example (Example 150). Coupled with the general knowledge in the art at the time of the invention, Applicants submit that the present application provides sufficient guidance to one skilled in the art to use the invention without undue experimentation. As the M.P.E.P. states, "The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-charge cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff. sub nom.*, *Massachusetts Institute of Technology v A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985) M.P.E.P. 2164.01. The Examiner is therefore, respectfully requested to reconsider and withdraw the rejection of these claims under 35 U.S.C. §112, first paragraph.

7. **Claim Rejections Under 35 U.S.C. §112, First Paragraph (Written Description)**

Claims 28-47 are rejected under 35 U.S.C. §112, first paragraph, for allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention at the time the application was filed. In particular, the Examiner notes that "[t]he claims are drawn to

polynucleotides having at least 80%, 85%, 90%, 95% or 99% sequence identity with SEQ ID NO:226 as well as vectors and host cells[, without requiring] that the polynucleotides or encoded polypeptides of the present invention possess any particular biological activity”

Applicants submit that the cancellation of Claims 36 and 37 renders the rejection of these claims moot.

Without acquiescing to the propriety of this rejection, solely in the interest of expediting prosecution in this case, Applicants respectfully submit that amended Claims 28-32 (and, as a consequence, those claims dependent from the same) now recite a functional limitation that the encoded polypeptide induces chondrocyte re-differentiation. Accordingly, it is no longer true that the claims are drawn to a genus of polynucleotides defined by sequence identity alone. Coupled with the general knowledge available in the art at the time of the invention, the specification provides ample written support for such polypeptides in Example 150 (page 512 of the specification) where assay for the ability of polypeptides to induce chondrocyte re-differentiation is described. Thus, based on the high percentage of sequence identity and the described method to assay for induction of chondrocyte re-differentiation, one skilled in the art would have known at the time of the invention, that the Applicants had possession of the claimed polynucleotides.

The Examiner is therefore respectfully requested to reconsider and withdraw the rejection of these claims for allegedly lacking written support.

8. Claim Rejections Under 35 U.S.C. §112, Second Paragraph

A. Claims 28-47 are rejected under 35 U.S.C. §112, second paragraph, for allegedly “being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.” The Examiner notes that Claims 28-47 are vague and indefinite since “it is not clear whether or not the protein encoded by the polynucleotide of the present invention is a soluble protein (*e.g.*, protease), nor is it disclosed as being expressed on a cell surface.” Accordingly, the Examiner asserts that the recitation of “extracellular domain” and the recitation of “the extracellular domain . . . lacking its associated signal sequence” are indefinite.

Without acquiescing to the propriety of this rejection, solely in the interest of expediting prosecution in this case, Applicants submit that the cancellation of Claims 36-37 and 41-47 renders the rejection of these claims moot. Further, terms "extracellular domain" and "extracellular domain ... lacking its associated signal sequence" are no longer present in Claims 28-32 (and, as a consequence, those claims dependent from the same).

Accordingly, Applicants request that the rejection of Claims 28-35, 38-40 and 44-47 under 35 U.S.C. §112, second paragraph, be withdrawn.

B. The Examiner alleges that Claims 41-43 are vague and indefinite since the claim recites "hybridizes" without the recitation of any conditions, or recites "stringent conditions" wherein these conditions are not known.

Without acquiescing to the propriety of this rejection, solely in the interest of expediting prosecution in this case, Applicants submit that the cancellation of Claims 41-43 renders the rejection of these claims moot.

9. Claim Rejections - 35 U.S.C. §102

Claims 28-47 are rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Lai *et al.* (U.S. Patent No. 5,932,442, filing date of September 23, 1997, issue date of August 3, 1999). The Examiner notes that "Lai teach a polynucleotide which which is 50.8% identical to SEQ ID NO:226... This nucleic acid molecule will hybridize to that of the present invention even under the most stringent conditions. Since the length of the extracellular domain is not known ... the limitations of 'at least 80%' are met."

First of all, Applicants respectfully submit that Lai *et al.* which was published less than a year before Applicants' priority date, cannot be cited as a reference under 35 U.S.C. §102(b). If the Examiner contends that Lai *et al.* is prior art, then it must be so under 35 U.S.C. §102(e).

Applicants respectfully submit that the cancellation of Claims 36-37 and 41-43 renders the rejection of these claims moot. Further, since the terms "extracellular domain" and "extracellular domain ... lacking its associated signal sequence" are no longer present in

Claims 28-33 (and, as a consequence, those claims dependent from the same), the rejection to these claims are believed to be moot.

Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

CONCLUSION

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited. Should there be any further issues outstanding, the Examiner is invited to contact the undersigned attorney at the telephone number shown below.

Applicants expressly reserve the right to pursue any canceled subject matter in subsequent continuation, divisional or continuation-in-part applications.

Please charge any additional fees, including fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-2830 P1C55**).

Respectfully submitted,

Date: November 10, 2004

By: 
Anna L. Barry (Reg. No. 51,436)

HELLER EHRMAN WHITE & McAULIFFE LLP
275 Middlefield Road
Menlo Park, California 94025-3506
Telephone: (650) 324-7000
Facsimile: (650) 324-0638

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**AMERICAN TYPE CULTURE COLLECTION**

10801 University Blvd.
Manassas, VA 20110-2209
Telephone: 703-365-2700
Fax: 703-365-2745

FACSIMILE

Date: October 7, 1998

To: Ginger R. Dreger
Genentech, Inc.

Fax Number: 650-952-9881

From: ATCC Patent Depository

Number of pages: 2
(Including this page)

REFERENCE: Patent Deposit

pINCY-based plasmid DNA66672-1586 (Ref. PR1586) assigned ATCC 203265,
pRK5E-based plasmid DNA71184-1634 (Ref. PR1634) assigned ATCC 203266,
pINCY-based plasmid DNA66667-1596 (Ref. PR1596) assigned ATCC 203267,
pINCY-based plasmid DNA66663-1598 (Ref. PR1598) assigned ATCC 203268,
pINCY-based plasmid DNA66659-1593 (Ref. PR1593) assigned ATCC 203269,
pINCY-based plasmid DNA73739-1645 (Ref. PR1645) assigned ATCC 203270,
pINCY-based plasmid DNA58852-1637 (Ref. PR1637) assigned ATCC 203271,
pINCY-based plasmid DNA66669-1597 (Ref. PR1597) assigned ATCC 203272,
pRK5D-based plasmid DNA73401-1633 (Ref. PR1633) assigned ATCC 203273,
pSPORT1-based plasmid DNA68879-1631 (Ref. PR1631) assigned ATCC 203274,
pINCY-based plasmid DNA71290-1630 (Ref. PR1630) assigned ATCC 203275,
pINCY-based plasmid DNA68864-1629 (Ref. PR1629) assigned ATCC 203276,
pINCY-based plasmid DNA68874-1622 (Ref. PR1622) assigned ATCC 203277,
pBluescript SK-based plasmid DNA64842-1632 (Ref. PR1632) assigned ATCC 203278,
pSPORT1-based plasmid DNA66660-1585 (Ref. PR1585) assigned ATCC 203279,
pINCY-based plasmid DNA68871-1638 (Ref. PR1638) assigned ATCC 203280,
pINCY-based plasmid DNA66674-1599 (Ref. PR1599) assigned ATCC 203281,
pINCY-based plasmid DNA66675-1587 (Ref. PR1587) assigned ATCC 203282,
pINCY-based plasmid DNA68866-1644 (Ref. PR1644) assigned ATCC 203283,
pSPORT1-based plasmid DNA71269-1621 (Ref. PR1621) assigned ATCC 203284, and
pINCY-based plasmid DNA71277-1636 (Ref. PR1636) assigned ATCC 203285.

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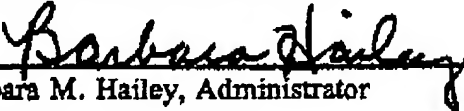
page 2.

Date of Deposit: September 22, 1998 . Paperwork will be forwarded to you in a few days.
An invoice will be sent under separate cover referencing P.O. 515441:

One time fee - 30 years	\$ 12,600.00
Informing fee - 30 years	
Viability Test	<u>3,150.00</u>

Total amount to ATCC 203265-203285	\$ 15,750.00
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Balance due to ATCC 203265-203285	\$ 15,750.00
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Barbara M. Hailey, Administrator
ATCC Patent Depository

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(203265-203285)

The fluorescence change from baseline to the maximum rise of the curve (Δ change) was calculated, and replicates averaged. The rate of fluorescence increase was monitored, and only those samples which had a Δ change greater than 1000 and a rise within 60 seconds, were considered positive.

The following PRO polypeptides tested positive in this assay: PRO1246 and PRO1561.

5 EXAMPLE 141: Skin Vascular Permeability Assay (Assay 64)

This assay shows that certain polypeptides of the invention stimulate an immune response and induce inflammation by inducing mononuclear cell, eosinophil and PMN infiltration at the site of injection of the animal. Compounds which stimulate an immune response are useful therapeutically where stimulation of an immune response is beneficial. This skin vascular permeability assay is conducted as follows. Hairless guinea pigs weighing 350 grams or more are anesthetized with ketamine (75-80 mg/Kg) and 5 mg/Kg xylazine intramuscularly (IM). A sample of purified polypeptide of the invention or a conditioned media test sample is injected intradermally onto the backs of the test animals with 100 μ l per injection site. It is possible to have about 10-30, preferably about 16-24, injection sites per animal. One μ l of Evans blue dye (1% in physiologic buffered saline) is injected intracardially. Blemishes at the injection sites are then measured (mm diameter) at 1 hr and 6 hr post injection. Animals were sacrificed at 6 hrs after injection. Each skin injection site is biopsied and fixed in formalin. The skins are then prepared for histopathologic evaluation. Each site is evaluated for inflammatory cell infiltration into the skin. Sites with visible inflammatory cell inflammation are scored as positive. Inflammatory cells may be neutrophilic, eosinophilic, monocytic or lymphocytic. At least a minimal perivascular infiltrate at the injection site is scored as positive, no infiltrate at the site of injection is scored as negative.

The following polypeptide tested positive in this assay: PRO1283, PRO1325 and PRO1343.

EXAMPLE 142: Induction of c-fos in Endothelial Cells (Assay 34)

This assay is designed to determine whether PRO polypeptides show the ability to induce c-fos in endothelial cells. PRO polypeptides testing positive in this assay would be expected to be useful for the therapeutic treatment of conditions or disorders where angiogenesis would be beneficial including, for example, wound healing, and the like (as would agonists of these PRO polypeptides). Antagonists of the PRO polypeptides testing positive in this assay would be expected to be useful for the therapeutic treatment of cancerous tumors.

Human venous umbilical vein endothelial cells (HUVEC, Cell Systems) in growth media (50% Ham's F12 w/o GHT: low glucose, and 50% DMEM without glycine: with NaHCO₃, 1% glutamine, 10 mM HEPES, 10% FBS, 10 ng/ml bFGF) were plated on 96-well microtiter plates at a cell density of 1×10^4 cells/well. The day after plating, the cells were starved by removing the growth media and treating the cells with 100 μ l/well test samples and controls (positive control = growth media; negative control = Protein 32 buffer = 10 mM HEPES, 140 mM NaCl, 4% (w/v) mannitol, pH 6.8). The cells were incubated for 30 minutes at 37°C, in 5% CO₂. The samples were removed, and the first part of the bDNA kit protocol (Chiron Diagnostics, cat. #6005-037) was followed, where each capitalized reagent/buffer listed below was available from the kit.

EXAMPLE 149: Detection of PRO Polypeptides That Affect Glucose or FFA Uptake by Primary Rat Adipocytes (Assay 94)

This assay is designed to determine whether PRO polypeptides show the ability to affect glucose or FFA uptake by adipocyte cells. PRO polypeptides testing positive in this assay would be expected to be useful for the therapeutic treatment of disorders where either the stimulation or inhibition of glucose uptake by adipocytes would be beneficial including, for example, obesity, diabetes or hyper- or hypo-insulinemia.

In a 96 well format, PRO polypeptides to be assayed are added to primary rat adipocytes, and allowed to incubate overnight. Samples are taken at 4 and 16 hours and assayed for glycerol, glucose and FFA uptake. After the 16 hour incubation, insulin is added to the media and allowed to incubate for 4 hours. At this time, a sample is taken and glycerol, glucose and FFA uptake is measured. Media containing insulin without the PRO polypeptide is used as a positive reference control. As the PRO polypeptide being tested may either stimulate or inhibit glucose and FFA uptake, results are scored as positive in the assay if greater than 1.5 times or less than 0.5 times the insulin control.

The following PRO polypeptides tested positive as stimulators of glucose and/or FFA uptake in this assay: PRO1265, PRO1283, PRO1279, PRO1303, PRO1306, PRO1325, PRO1565 and PRO1567.

The following PRO polypeptides tested positive as inhibitors of glucose and/or FFA uptake in this assay: PRO1194, PRO1190, PRO1326, PRO1343, PRO1480, PRO1474, PRO1575 and PRO1760.

EXAMPLE 150: Chondrocyte Re-differentiation Assay (Assay 110)

This assay shows that certain polypeptides of the invention act to induce redifferentiation of chondrocytes, therefore, are expected to be useful for the treatment of various bone and/or cartilage disorders such as, for example, sports injuries and arthritis. The assay is performed as follows. Porcine chondrocytes are isolated by overnight collagenase digestion of articular cartilage of metacarpophalangeal joints of 4-6 month old female pigs. The isolated cells are then seeded at 25,000 cells/cm² in Ham F-12 containing 10% FBS and 4 µg/ml gentamycin. The culture media is changed every third day and the cells are then seeded in 96 well plates at 5,000 cells/well in 100 µl of the same media without serum and 100 µl of the test PRO polypeptide, 5 nM staurosporin (positive control) or medium alone (negative control) is added to give a final volume of 200 µl/well. After 5 days of incubation at 37°C, a picture of each well is taken and the differentiation state of the chondrocytes is determined. A positive result in the assay occurs when the redifferentiation of the chondrocytes is determined to be more similar to the positive control than the negative control.

The following polypeptide tested positive in this assay: PRO1265, PRO1250, PRO1430, PRO1356, PRO1275, PRO1274, PRO1286, PRO1273, PRO1283, PRO1279, PRO1306, PRO1325, PRO1343, PRO1418, PRO1565, PRO1474, PRO1787, PRO1556 and PRO1801.

EXAMPLE 151: Induction of Pancreatic β-Cell Precursor Proliferation (Assay 117)

This assay shows that certain polypeptides of the invention act to induce an increase in the number of pancreatic β-cell precursor cells and, therefore, are useful for treating various insulin deficient states in mammals, including diabetes mellitus. The assay is performed as follows. The assay uses a primary culture of mouse fetal pancreatic cells and the primary readout is an alteration in the expression of markers that represent

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